Altered long-range temporal correlations of alpha-oscillations in limbic and attentional systems predict depression severity

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Tiivistelmä – Referat – Abstract

Introduction and aims. Multiple different neurobiological alterations have been hypothesized to underlie Major Depression Disorder (MDD), but no unifying theory exists to explain the mechanisms of the disorder. The aberrant brain dynamics in MDD can be seen in the alterations of long-range temporal correlations (LRTCs), which have been proposed to be an indication of criticality in healthy brain. Alterations in LRTCs have been suggested to reflect deficiencies in excitation-inhibition (E/I) balance, neuromodulation or connectivity patterns, which have also been proposed to be the underlying mechanisms of MDD. There has been controversy whether the pathology is related to attenuated or increased LRTCs, and the sources of altered brain dynamics have not yet been localized.

The aim of this study was to find in which frequency bands and where in the brain the neuronal LRTCs are altered in MDD on source level. In addition to analyzing the correlations between neuronal LRTCs and depression severity in parcel level, we studied correlations in functional networks to get a better understanding of the system level alterations in MDD. We also studied whether behavioral LRTCs correlate with depression severity or with behavioral performance.

Methods. We investigated the long-range temporal correlations in a cohort of 19 depressed subjects by using magnetoencephalography (MEG) for recording brain activity during resting state and response inhibition task and performed DFA analysis on the amplitude envelopes of cortical oscillations. The depression severity was measured with BDI-21 questionnaire

Results and conclusions. We found the LRTCs to be positively correlated with depression severity in the alpha frequency band (8–12Hz) predominantly in the limbic system that underlies emotional control. This result was supported by the parcel level analysis in which correlations between alpha band LRTCs and depression severity were observed in the orbitofrontal cortex and temporal pole, indicating that the hyper-activation of limbic system could explain the negative bias characteristic to depression. Positive correlations were also found in frontoparietal, ventral, and dorsal attentional networks that support cognitive control.

Alpha band LRTCs correlated also with behavioral LRTCs during both resting state and task conditions. However, we observed more wide-spread correlations between alpha range LRTCs and depression severity than between neuronal LRTCs and behavioral LRTCs. Behavioral LRTCs correlated with depression severity, but not with behavioral performance. These results indicate that depression is characterized by vast alterations in the brain dynamics and imply that the wide range of different symptoms in MDD could be explained by alterations in the excitation/inhibition balance in the limbic system and cognitive networks.

Avainsanat – Nyckelord – Keywords
alpha-oscillations, long-range temporal correlations, magnetoencephalography, major depressive disorder

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Tiivistelmä – Referat – Abstract

Tausta ja tavoitteet. Masennuksen (Major Depression Disorder, MDD) taustalla on ehdotettu olevan lukuisia eri neurobiologisia häiriöitä mutta yhtenevää sairauden mekanismeja selittävää teoriaa ei ole pystytty luomaan. Aivojen poikkeava toiminta masennuksessa voidaan havaita muutoksina pitkäkestoisissa ajallisissa korrelaatioissa (Long Range Temporal Correlations, LRTC:t). LRTC:iden muutoksien on ehdotettu heijastavan häiriöitä eksitaatio/inhibitio -tasapainossa, neuromodulaatiossa tai konnektiivisuudessa. Aikaisempien tutkimustuloksien perusteella on epäselvää, liittyykö masennukseen vähentyneitä vai lisääntyneitä LRTC:itä. Dynamiikan muutoksia on toistaiseksi tutkittu ainoastaan sensoritasolla eikä niitä ole paikannettu aivoissa.

Tämän tutkimuksen tavoite oli selvittää missä taajuuskaistoissa ja millä aivoalueilla LRTC:t ovat häiriintyneet masennuksessa. Erillisten aivoalueiden lisäksi LRTC:iden ja masennuksen vakavuuden välistä korrelaatiota tutkittiin myös toiminnallisissa verkostoissa, pyrkimyksenä lisätä ymmärrystä masennukseen liittyvistä systeemitason häiriöistä aivoissa. Myös reaktioaikojen LRTC:iden mahdollista yhteyttä masennukseen ja suoritustasoon selvitettiin.

Menetelmät. Yhdeksäntoista koehenkilön aivokuoren oskillaatioita mitattiin lepotilan ja toiminnan estämistä mittaavan tehtävän aikana magnetoenkefalografian (MEG) avulla ja pitkäkestoisia ajallisia korrelaatioita tutkittiin DFA-analyysin avulla. Koehenkilöiden masennuksen vakavuutta mitattiin BDI-21 -masennuskyselyllä.

Tulokset ja johtopäätökset. LRTC:iden havaittiin korreloivan positiivisesti masennuksen vakavuuden kanssa alpha-taajuudella (8–12Hz) pääasiallisesti limbisessä järjestelmässä, joka vastaa tunteiden säätelystä. Tulosta tukee erillisten aivoalueiden tasolla tehty analyysi, jossa alpha-taajuuskaistan LRTC:iden huomattiin korreloivan masennuksen kanssa orbitofrontaalisessa aivokuoressa ja temporaalisessa lohkossa. Tämä osoittaa, että limbisen järjestelmän yliaktiivisuus saattaa selittää masennuksessa ilmenevän negatiivisen vääristymän ajattelussa. Positiivisia korrelaatioita havaittiin lisäksi frontoparietaalisessa verkostossa, sekä ventraalisessa ja dorsaalisessa tarkkaavaisuudesta vastaavissa verkostoissa, jotka tukevat kognitiivista säätelyä.

Alpha-taajuuskaistan LRTC:t korreloivat myös reaktioaikojen LRTC:iden kanssa lepotasomittauksen ja tehtävän aikana. Korrelaatioita alpha-taajuuskaistan LRTC:iden ja depression välillä havaittiin kuitenkin laajemmalla alueella kuin alpha-taajuuskaistan LRTC:iden ja reaktioaikojen LRTC:iden välisiä korrelaatioita. Lisäksi reaktioaikojen LRTC:t korreloivat masennuksen kanssa mutta korrelaatiota ei havaittu reaktioaikojen LRTC:iden ja suoritustason välillä.
Näiden tuloksien perusteella voidaan päätellä, että masennukseen liittyy laajoja muutoksia aivojen toiminnan dynamiikassa, ja että taudin erilaisten oireiden kirjo voidaan selittää eksitaation ja inhibition välisen tasapainon muutoksilla limbisissä ja kognitiivisissa verkostoissa.

Avainsanat – Nyckelord – Keywords
alpha-oskillaatiot, pitkäkestoiset ajalliset korrelaatiot, magnetoenkefalografia, masennus

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Muita tietoja – Övriga uppgifter – Additional information

Preface

This study was conducted as a part of “Testing the efficacy of a novel computer-game-based treatment for major depressive disorder” project in the University of Helsinki and was financially supported by the Academy of Finland and Kela. I would like to thank my supervisor Prof. Matias Palva (PhD) for the opportunity to work in this project and for all the help during the process. Thank you also Prof. Satu Palva (PhD) for the help in the data analysis, and for Hanna Julku (MSc), Anna Lampinen (BA), and Santeri Rouhinen (PhD) for recording the MEG data.

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In Helsinki 12.7.2019

Birgitta Paranko

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1. Introduction

1.1 Long-range temporal correlations and criticality

Everyday life requires constant adaptation to the environment. Things like reacting to external stimuli require a flexible system that is capable of changing constantly. On the other hand, stability is required as the brain must be able to learn and form long-term memories that allow us to make predictions about the world. Hence the brain must operate in a state where it is capable of both reacting to changing stimulus and remembering things. It has been shown that neuronal oscillations show long-range temporal correlations, indicating that the brain dynamics are indeed not random but that there are temporal correlations on different time (Linkenkaer-Hansen, K., Nikouline, Palva, & Ilmoniemi, 2001) , possibly explaining our capability to both adapt and remember things simultaneously.

It has been suggested based on that the optimal information capacity and transmission in the brain are obtained in a critical state (Linkenkaer-Hansen et al., 2001; Shew, Yang, Yu, Roy, & Plenz, 2011). One of the fundamental properties of critical systems is that the interaction between simple components causes the emergence of long-range spatiotemporal correlated patterns. In these systems the behavior of the individual components is no longer only determined by the neighboring components, but also by the behavior of the population as a whole (Chialvo, 2010).

The two-way effect between individuals can be seen for example in the behavior of flocks of starlings. The collective behavior of the flock is not obtained through a leader, but through scale-free correlations across the whole group. Each individual affects even the furthest member of the flock through the information transfer that emerges from interindividual interactions, and each individual is affected by the behavior of the flock. Consequently, the flock can respond to changing environmental demands, such as a predator, as one. The correlations between the behavior of the individuals are referred as scale-free, because the length of the correlations is not limited to a specific group size, but the correlations can be seen in groups of all sizes (Cavagna et al., 2010).

This kind of self-organized scale-free dynamics have been shown to emerge spontaneously in many phenomena in the nature, such as in the species evolution, bacterial populations and forest fires (Bak, 1997; Gregoire & Prigogine, 1977; Malamud, Morein, & Turcotte, 1998).

1.2 Neuronal avalanches and long-range temporal correlations

It has been shown that the brain has scale-free dynamics, suggesting that it might operate close to a critical state. On a small scale, scale-free dynamics have been shown to exist in neuronal populations. In so called avalanches the activity of one neuron activates surrounding neurons causing a network effect. The probability of a small avalanche is higher than the probability of big avalanche, as the propagating activity does not always cause a network level effect, and the sizes of avalanches have been shown to follow an inverse power law in in vivo cortical slices. This suggests that the avalanches arise as a consequence of critical branching which optimizes the information transmission in a feed-forward network without the risk of runaway excitation (Beggs & Plenz, 2003).

On the level of bigger neuronal populations, the activity can be studied in the form of oscillations recorded with electro- and magnetoencephalography (M/EEG). Both MEG and EEG can be used to obtain temporally accurate information about the brain activity. EEG signals are produced by the electrical field potentials produced by active pyramidal cell populations, whereas MEG signals are produced by the changes in the magnetic fields, caused by the same electrical activity. MEG is not sensitive to radially oriented currents and this limits its use in the recording of signals originating from the top of the gyri, but it has slightly better spatial resolution than EEG, because the magnetic fields are not influenced by the changes in the electric conductivity between the brain, skull and scalp (Peter Hansen, Morten Kringelbach, Riitta Salmelin, 2010).

It has been shown that on long time scales (10^0 − 103 seconds) the amplitude envelopes of spontaneous neuronal oscillations recorded with M/EEG are scale-free and have long-range temporal correlations (LRTCs) (Linkenkaer-Hansen et al., 2001). The scaling exponents of the neuronal LRTCs and avalanches have been shown to be correlated (Palva et al., 2013; Zhigalov, Arnulfo, Nobili, Palva, & Palva, 2015) and it has been suggested both M/EEG amplitude fluctuations and avalanches emerge from an E/I

balance and share a common neural basis (Poil, Hardstone, Mansvelder, & Linkenkaer-Hansen, 2012). The human alpha band LRTCs in the visual and parietal cortices can be manipulated by pharmacological administration of catecholaminergics, and computational simulations suggest that these alterations in scale-free dynamics happen due to an increase in excitatory activity in relation to inhibitory activity (Pfeffer et al., 2018). Furthermore, it has been shown in cortical cultures that balanced excitation/inhibition (E/I) ratio allows the system to operate near criticality and maximizes the information processing capacity (Shew et al., 2011).

The scaling laws of LRTCs are not unique for M/EEG recordings, but slow fluctuations in blood oxygenation level-dependent (BOLD) signals recorded with functional magnetic resonance imaging (fMRI) have corresponding scale free properties (He, B. J., 2011). Furthermore, behavioral performance fluctuations follow power laws (Gilden, Thornton, & Mallon, 1995) and behavioral LRTCs in audiovisual threshold stimulus detection tasks have been shown to correlate with both neuronal avalanches and LRTCs derived from M/EEG in both resting state and task condition, as well as with LRTCs from a task that is based on a different sensory modality (Palva et al., 2013). LRTCs have been shown to be consistent in individuals between different measurements (Nikulin & Brismar, 2004) and the inter-subject variability has been shown to correlate with genetic differences (Linkenkaer-Hansen, Klaus et al., 2007). Altogether these results indicate that the fluctuations are endogenous and do not only reflect the brain activity that is related for example to motor responses during a task (Palva et al., 2013).

1.3 Altered LRTCs in depression

Alterations in LRTCS have been linked to several psychological and brain disorders such as epilepsy (Parish et al., 2004), Alzheimer's disease (Montez et al., 2009), schizophrenia (Nikulin, Jönsson, & Brismar, 2012) and migraine (Hodkinson, Lee, Becerra, & Borsook, 2019). Several studies have also studied the role of aberrant LRTCs in Major Depression Disorder (MDD), but the results have been conflicting. Both increased and attenuated LRTCs have been observed in depressed patients in comparison to healthy controls (Table 1 in Supplementary Materials), and both negative and positive correlations between

LRTCs and depression severity have been found in varying frequency bands. The analysis has been restricted to sensor level and no source level analysis has been reported.

The first observations of altered LRTCs in MDD indicated a negative correlation between MEG resting state LRTCs and depression severity (Linkenkaer-Hansen, Klaus et al., 2005). In this cohort, the depressed subjects had LRTCs close to 0.5, suggesting very low temporal correlations in the 5–100 seconds time range, whereas healthy controls had significantly higher values. Analysis was restricted to occipitoparietal and temporocentral regions, and only gradiometers were analyzed. Attenuated theta (3-7 Hz) band LRTCs were observed in the MDD group in comparison to the healthy controls (HC) in all of the analyzed areas, whereas differences in beta (15–29 Hz) band LRTCs were seen only in the temporocentral regions. Furthermore, depression severity was also shown to have a negative correlation with theta LRTCs in the left temporocentral region. In contrast, a slight positive correlation with alpha LRTCs in the occipitoparietal region was observed. It was later suggested by the authors that the attenuated values of theta and beta band LRTCs might be due to decrease in attention during the relatively long 16-minute resting state recording (Gärtner et al., 2017) and most of the following studies have shown a positive correlation between depression severity and increased LRTCs.

A positive correlation between depression severity and broad band (0.6–46 Hz) LRTCs was observed over most of the cortex in a five-minute eyes-closed resting state EEG measurement in a cohort of 11 medication-free MDD subjects (Lee et al., 2007). The LRTCs were also significantly higher in the patient group in comparison to the healthy controls in temporal regions on both hemispheres and left hemisphere structures.

In addition, MDD patients (N=71) have been shown to have increased theta (4–7 Hz) band LRTCS in eyes-closed resting state in mid and left frontal as well as left temporal electrode sites in comparison to healthy controls (N=25) (Gärtner et al., 2017). Improvements in the symptoms after a two-week mindfulness meditation treatment were correlated with the reduction in the post-treatment theta frequency LRTCs. The changes were observed in the central and temporal regions, especially on the left hemisphere. Another subgroup of the patients went through a stress-reduction treatment and this decreased the LRTCs in the

fronto-parietal midline region, but the change was not correlated with decrease in symptoms.

Broad band (1–40 Hz) and theta (3–7 Hz) band LRTCs have been shown to be related to depression severity also in sub-clinically depressed subjects (Bornas, Fiol-Veny, Balle, Morillas-Romero, & Tortella-Feliu, 2015). Correlations with depression severity were found in broad band LRTCs in central and parietal areas, and in the theta LRTCs in the parietal sites. In contrasts, alpha (8–13 Hz) band LRTCs were observed to have negative correlations with depression severity in the frontal, central, occipital and temporal regions. In addition, negative emotion regulation strategies, such as brooding and thought suppression, were shown to have positive correlation with broad band LRTCs and negative correlation with theta and alpha band LRTCs. No differences were found between sub-clinically depressed subjects and non-depressed subjects. The measurement consisted of eight-minute resting state measurement with alternating two-minute periods of eyes-closed and -open intervals. Clinically depressed participants were excluded.

Aberrant broad band and theta LTRCs have previously been shown to have positive correlations with maladaptive emotion regulation strategies by the same authors (Bornas et al., 2013), and the conflicting results between the two studies were hypothesized to be explained by the inadequate screening of depression symptoms in the earlier study. Similarly, the use of maladaptive emotion regulation strategies in healthy control groups might explain why significant difference between MDD and healthy controls is always not observed, as was the case in a cohort of 45 MDD subjects and 45 HC in a five-minute resting state data (Hosseinifard, Moradi, & Rostami, 2013). In this study it was observed that alpha band power and correlation dimension are more effective ways of classifying MDD patients and HC than LRTCs.

A variety of time windows ranging from 0.1s–6 seconds to 5–100 seconds was used in the different studies. Short time windows can bias the estimates of the LRTCs (Hu, Ivanov, Chen, Carpena, & Stanley, 2001; Kantelhardt, Koscielny-Bunde, Rego, Havlin, & Bunde, 2001) and this might explain the conflicting results. Some of the differences can also probably be explained by the different methods that were used to obtain the data, as the studies contain both EEG and MEG data and the number of EEG channels varied between the studies.

1.4 Altered excitation-inhibition balance in depression

Depression has been linked to a wide range of different underlying neurobiological mechanisms, such as altered neurotransmission, HPA axis abnormalities in response to stress, inflammation, reduced neuroplasticity and network dysfunction (Dean & Keshavan, 2017). We will here concentrate on alterations in excitation-inhibition (E/I) balance as it not only underlies alterations in LRTCs but has also been suggested to be one of the core neurobiological mechanisms of depression.

A wide range of studies done in both mice and people supports the role of E/I balance in MDD. In a cohort of 33 MDD subjects and 38 controls proton magnetic resonance spectroscopy was used to show that there is a decrease in the GABA concentration and increase in glutamate concentration in the occipital cortex of MDD subjects in comparison to healthy subjects (Sanacora et al., 2004). Only occipital cortex was investigated because of technical limitations. This was a replication of earlier results with a smaller cohort (Sanacora et al., 1999) and indicates that there is an imbalance between excitatory and inhibitory neurotransmitter levels in the cortex of MDD patients. Later it has been shown that the alterations extend also to dorsomedial/dorsal anterolateral prefrontal and ventromedial prefrontal areas (Hasler et al., 2007), and that the GABA levels stay low even after recovery in the occipital and anterior cingulate cortex (Bhagwagar et al., 2008).

Genetic post-mortem studies on depressed suicide victims support GABA's role in MDD. The expression of $GABA_AR$ subunit transcripts has been shown to be altered in suicidal subjects in comparison to subjects who died because of natural causes (Luscher, Shen, & Sahir, 2011). The subunit expression levels can also be altered by epigenetic mechanisms. It has been shown in rodent models that both enhanced and decreased maternal care affects the $GABA_A$ receptor mRNA subunit expression in brain regions that regulate stress responses, including amygdala, prefrontal cortex, hippocampus, and locus coeruleus (Caldji, Diorio, & Meaney, 2003).

GABA subunit alterations have also been shown to have a causative effect on depression, as global and forebrain-specific heterozygous inactivation of the $gamma_2$ subunit gene in the mouse embryos increased the corticosterone concentration and anxious-depressive behavior (Shen et al., 2010). Furthermore, it has been observed that pharmacological

administration of antidepressant Rebotexine (selective norepinephrine reuptake inhibitor) to stressed male rats reduces GAD67 mRNA in the central limbic stress circuits (Herman, Renda, & Bodie, 2003), indicating that one of the mechanisms of antidepressants could be the normalization of the altered E/I balance.

The E/I balance theory of MDD is also well in line with the neurotrophic hypothesis of MDD, just looking at the same phenomena from a different perspective. The neurotrophic hypothesis states that MDD is associated with decreased levels of neuronal plasticity, and the effects of antidepressants take place via increasing the BDNF levels and neuronal plasticity (Bus & Molendijk, 2016). On the other hand, BDNF has been shown to alter the E/I balance in the rodent hippocampus and prefrontal cortex by increasing the phosphorylation, activity, and cell-surface stability of $GABA_A$ receptors within minutes of application (Jovanovic, Thomas, Kittler, Smart, & Moss, 2004). Antidepressant Fluoxetine has also been shown to reorganize inhibitory circuits in the amygdala by increasing the expression of a plasticity related form of neural cell adhesion molecule (PSA-NCAM) (Carceller, Perez-Rando, Castren, Nacher, & Guirado, 2018).

These results suggest that both plasticity and inhibitory networks are altered in depression and that they can be modified by antidepressant Fluoxetine at least in rodents. The changes have been localized to the areas in the limbic system, suggesting that the alterations in E/I balance in systems that regulate emotions might be one of the underlying mechanisms of depression.

1.5 Study aims

Both depression and altered LRTCs have been suggested to share the same underlying mechanism, and alterations in LRTCs have been shown to characterize MDD. However, the results so far have been conflicting, giving support for both attenuated and increased LRTCs in MDD.

The aim of this study was to find in which frequency bands and where in the brain the neuronal LRTCs are altered in MDD on source level. In addition to analyzing the correlations between neuronal LRTCs and depression severity in parcel level, we wanted to study correlations in functional networks to get a better understanding of the system

level alterations in MDD. We also wanted to know whether behavioral LRTCs correlate with depression severity or with behavioral performance.

2. Materials and Methods

2.1 Participants

22 participants were recruited in cooperation with Helsinki University Hospital (HUS) via Mental Hub (www.mielenterveystalo.fi), and social media. Resting state data was analyzed for 19 subjects and task data for 18 subjects. Three subjects had to be excluded from the data analysis because of missing MRIs that were required for source localization and one subject was excluded from the task analysis because of missing answers. The experiment was undertaken with the understanding and written consent of each subject, and the experiment was approved by the ethical committee of HUS. The study was performed according to the Declaration of Helsinki (World Medical Association).

The participants were 19–45 years old (12 female; 19 right-handed; 14 had antidepressant medication, mean age 33.5 and range 19–45) and the severity of their depression was evaluated by using a BDI-21 questionnaire (Beck & Beamesderfer, 1974). Participants who did not fulfil the depression criteria (BDI-21 score less than ten) at the time of registration or who had current suicidal intentions were excluded from the study. Participants were also screened for comorbidities, including alcohol abuse, anxiety disorder, bipolar disorder, borderline personality disorder and mania, but these were not used as exclusion criteria. The participants' demographics and clinical data are summarized in Table 1. Depression scores at the time of MEG-measurements ranged from four to 38 (Figure 1).

Table 1. Demographic information.	
Sex (female/male)	12/7
Age (mea [range])	33.5 [19,45]
BDI-21 (mean [range])	23.8 [4,38]

BDI-21: 21-item Beck Depression Inventory (Beck & Beamesderfer, 1974), scoring from 0 to 63

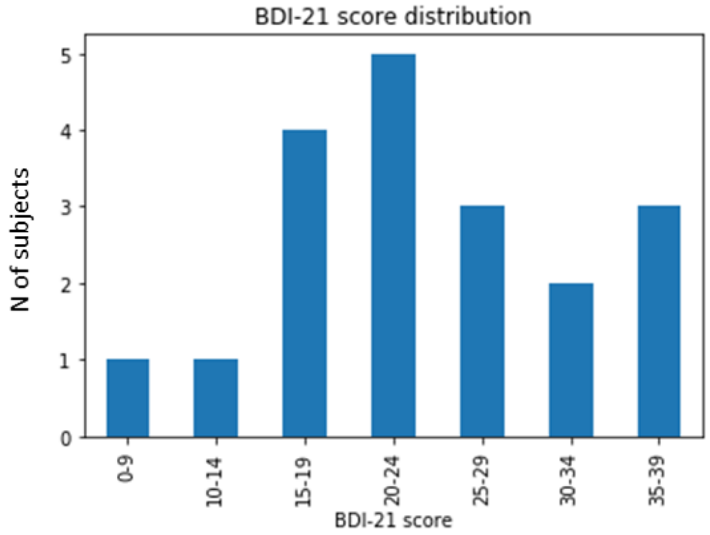

Figure 1. BDI-21 score distribution. Suicidal participants were excluded, and the cohort does not include the extreme end of the severe depression, the maximum score being 38. One sub-clinical participant was included in the cohort, as he/she fulfilled the depression criteria at the time of the requirement.

2.2 Cognitive Go/NoGo task

The MEG session consisted of a ten-minute eye-open resting state recording and two 18-minute cognitive Go/NoGo response inhibition tasks. The order of the response-inhibition tasks was counterbalanced between the participants. Only resting state and FB condition data were analyzed in this this study.

In the Go/NoGo FB task blue and yellow squares were projected on the screen in 1s intervals. The target was visible for 100 milliseconds and the participants were instructed to maintain fixation to a fixation cross between the stimuli. The participants were instructed

to lift their right index finger when they saw a blue square and to ignore the yellow squares.
Correct responses to the Go stimuli were defined as hits and responses following NoGo stimulus were defined as false alarms (FA).

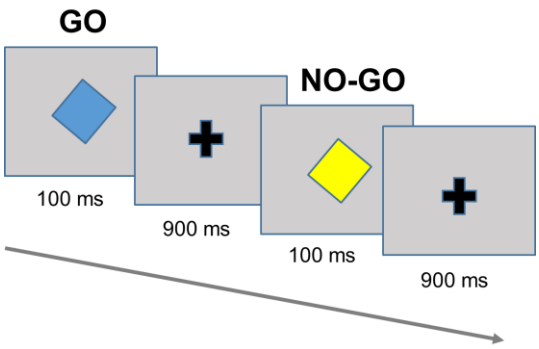

Fig 2. Go/NoGo FB paradigm. Task consisted of Go and NoGo signals that were presented in 1s intervals and the participant had to response to the Go signals and inhibit the response when NoGo signal was presented.

2.3 MEG and MRI recordings

The MEG recordings were performed in BioMag laboratory of the Helsinki University Hospital with a 306 channel Elekta TRIUX Neuromag MEG instrument composed of 204 planar gradiometers and 102 magnetometers at 600 Hz sampling rate. Eye movement was recorded with electro-oculogram (EOG) for artefact control.

T1-weighted anatomical MRIs for cortical surface reconstruction were obtained for each subject at a resolution of a 1 × 1 × 1 -mm^3 (MP-RAGE) with a 1.5 Tesla MRI scanner (Siemens). The flip angle was set to eight, echo time to 2.47, and repetition time to 2200.

2.4 Signal processing

MRIs were processed with Freesurfer software (http://surfer.nmr.mgh.harvard.edu/). This included automatic volumetric segmentation of the data, surface reconstruction, cortical

parcellation, and labeling with the Destrieux atlas (Dale et al., 2000; Destrieux, Fischl, Dale, & Halgren, 2010; Lin, Belliveau, Dale, & Hämäläinen, 2006) Three-layer boundary element models (BEMs), cortically constrained source models, MEG-MRI- co-localization and preparation of the forward and inverse operators (Gramfort et al., 2014; Hämäläinen & Ilmoniemi, 1994) were made with MNE software (http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php).

MEG data was processed with LabVIEW-based (National Instruments) neuroinformatics platform. Bad channels were removed by using the Elekta Neuromag MaxFilter(TM) (version 2.2.15) (Taulu, S. & Simola, 2006; Taulu, Samu & Kajola, 2005). Head position indicator (HPI) coil signals were not filtered from the data as should have been done in this step, and the non-filtered data was used for the current study.

Components associated with eye movements/blinks and cardiac artefacts were identified and removed using FieldTrip MATLAB toolbox independent component analysis (ICA) (Oostenveld, Fries, Maris, & Schoffelen, 2011). The pre-processed MEG time series from each separate channel were transformed into time-frequency domain using the continuous wavelet transform with Morlet wavelets into 38 bands (m=5, 3–143Hz).

To measure noise levels in each experiment, noise covariance matrices (NCMs) were computed by using broad band filtering (nominal frequency 225Hz). Synthetic events were added in five second intervals to the resting state data and these events were used to compute NCMs. In the Go/NoGo data one-minute resting state preceding the task was used for the NCM. The same filters were also used for creating fidelity weighted inverse operators.

Forward and inverse modelling was obtained to approximate the sources of the signals. Each sensor receives signals from multiple sources and one signal can be seen in multiple sensors. Hence a model is needed for approximating the original sources of the signals that are seen on the sensor-level. A forward model is used for creating a simulation of sensor-level activation. This is then used for creating a model that approximates the original source-level activation. The predictions of the model are compared to the original source-level activation, and each sensor is given a fidelity weight ranging from zero to one

based on its predictive power. The fidelity weighted inverse model is then created by using the best sensors (Hansen et al., 2010).

Source time series were collapsed into optimized cortical parcellations of 400 patches (Korhonen, Palva, & Palva, 2014), hereafter referred as parc2009 400AFS parcellation. Parcels were also morphed to Yeo7 functional networks which have been defined with fMRI (Thomas Yeo et al., 2011). The networks include visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default networks, and their topography is shown in Figure 5B.

2.5 DFA analysis

The LRTCs for cortically reconstructed source time series and reaction time -time series were quantified using detrended fluctuation analysis (DFA).

In the DFA analysis the timeseries is normalized to zero mean and integrated. The integrated signal is then segmented into multiple time windows with varying sizes Δt. Each segment of integrated data is then locally fitted to a linear function $y_{\Delta t}$ and the mean-squared residual F(Δt) is computed:

$$\mathrm{F}(\Delta \mathrm{t}) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - \mathrm{y}_{\Delta \mathrm{t}}(\mathrm{k})]^2}$$

Where N is the length of the time series.

The slope of the linear regression of the function F(Δt) in log-log coordinates can be used as a measure for LRTCs. Values close to 0.5 are associated with uncorrelated white noise and higher values of LRTCs are a sign for stronger temporal dependencies.

Neuronal LRTCs were obtained by applying DFA to the amplitude envelope of the processed MEG signal for each cortical patch and frequency band separately in the resting state and Go/NoGo condition. Window sizes from 1 to 225 seconds were used.

DFA analysis of the behavioral data on the Go/NoGo task was done by following the pipeline of Simola, Zhigalov, Morales-Muñoz, Palva, & Palva (2017). Both hits and false

alarms were included into the RT timeseries, as it was previously shown that removing FAs did not change the scaling exponents effectively (Simola, Zhigalov, Morales-Muñoz, Palva, & Palva, 2017). Extreme RT values (<150 ms and >800ms) were excluded as was done previously.

2.6 Correlation with clinical symptoms and behavioral performance

The correlations of the neural fluctuation scaling law exponents with BDI-21 scores, FA rates and RT scaling exponents were analyzed separately in resting state and Go/NoGo condition. A one-tailed Spearman rank correlation was used to determine significant correlations in both parc2009 400AFS parcels and parc2011 Yeo7 functional networks ($p<0.05$). FDR (alpha=0.05) was used for correcting the statistics for multiple testing.

Correlations were calculated for each frequency band separately. The highest fraction of significant correlations between neural LRTCs and depression severity after correction for multiple testing with FDR was observed in the frequencies within the alpha band (8.14, 9.02, 9.83, 10.92 and 11.89 Hz) (Figure 4), and alpha band was chosen for further analysis based on this.

The correlations were visualized on an inflated cortical surface with PySurfer software (https://pysurfer.github.io/). The colors indicate the average of the significant ($p<0.05$, FDR corrected) one tailed Spearman rank correlations between the LRTCs in the alpha band frequencies and BDI-21 score, reaction time LRTCs and FAs.

3. Results

3.1 Depression severity has a negative correlation with False alarm rate and positive correlation with reaction time LRTCs

False alarm rates were found to have a negative correlation with BDI-21 scores (rho=-0.49, p=0.04, two-tailed Spearman rank correlation) (Figure 3A). FA did not correlate

significantly with age (rho=-0.10, p=0.68, two-tailed Spearman rank correlation) or years of education (rho=-0.10, p=0.69, two-tailed Spearman rank correlation).

Signal detection theory was used to rule out the role of differences in tendency to respond, and no significant correlations between criterion values and depression severity was found (rho=0.326, p=0.160, two-tailed Spearman rank correlation), indicating that the relationship between depression severity and performance cannot be explained with decreased risk-taking or decreased motor activity levels in depression.
This study was conducted as part of a depression gaming study, and hence also the average weekly gaming hours were recorded. However, the better performance of the severely depressed participants was not explained by experience in gaming, as there was no significant correlation between gaming hours and FA rate (rho=0.14, p=0.59, two-tailed Spearman rank correlation).

Reaction time LRTCs were found to correlate with BDI-21 scores (rho=0.48, p=0.045, two-tailed Spearman rank correlation) (Figure 3B). Mean reaction times or hit rates were not found to correlate with depression severity (rho= -0.09, p=0.71 and rho=0.09, p=0.72 respectively, two-tailed Spearman rank correlation).

It should also be noted that the significant correlations between BDI-21 and FA rate and RT LRTCs are lost if corrected for multiple comparison when testing the correlations with other questionnaires. In addition, RT LRTCs did not correlate significantly with FA rates (rho=-0.25, p=0.32, two-tailed Spearman rank correlation).

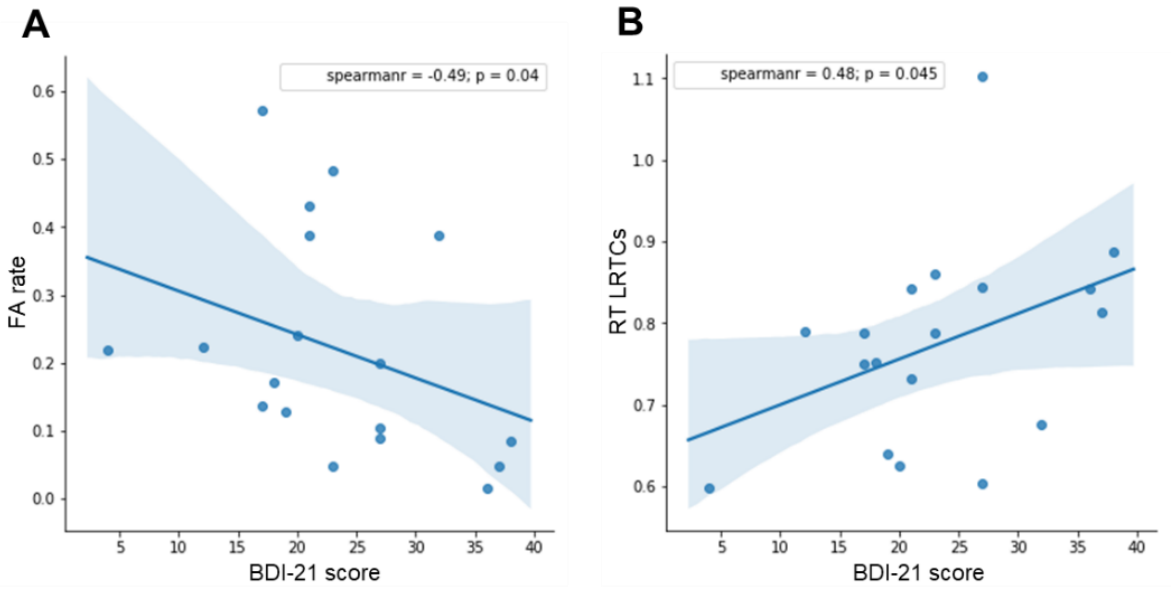

Figure 3. BDI-21 score correlations with False alarm rate and reaction time LRTCs in the Go/NoGo task. **A)** FA rate has a negative correlation with BDI-21 score (rho=-0.49, p=0.04, two-tailed Spearman rank correlation), indicating that severe depression is linked to lower level of errors. **B)** RT LRTCs have a positive correlation with depression severity (rho=0.48, p=0.045, two-tailed Spearman rank correlation).

3.2 Alpha band LRTCs correlate with depression severity in limbic system and ventral visual attention network

The correlations of LRTCs with BDI-21 score were first analyzed in parc2009 400AFS parcels. In both conditions, the highest fraction of significant correlations was in the alpha range (8–12Hz) frequencies ($p<0.05$, FDR corrected, one-tailed Spearman rank correlation). In resting state the highest fraction of significant correlations was 0.0975 (freq=9.83 Hz) and in Go/NoGo it was 0.1575 (freq=9.83Hz) (Figure 4A).

Almost half (47%) of the parcels where significant correlations were found in resting state reached significance also in the Go/NoGo task. The parcels where alpha band LRTCs correlated with BDI-21 scores in both conditions were predominantly located in the occipital, temporal, parietal and orbital areas, and parts of the insula. Interestingly, some areas, such as occipital-temporal regions in the right hemisphere had significant correlations with depression severity in the resting state, but not during the task condition. In the inhibition task, also parts of anterior cingular cortex, right dorsal precuneus, and

parts of occipital, occipital-temporal lobe and frontal areas in the left hemisphere correlated with depression severity (Figure 5A).

Correlations were also studied in the Parc2011Yeo7 functional networks (Thomas Yeo et al., 2011). In both conditions, the highest fraction of significant correlations was in the alpha range frequencies ($p<0.05$ and FDR corrected, one-tailed Spearman rank correlation). In resting state the highest fraction of significant correlations was 0.0625 (freq=9.83, 10.92 and 30.8 Hz) and in the Go/NoGo data it was 0.1875 (freq=10.92 Hz) (Figure 4B).

Alpha band LRTCs were found to be significantly correlated with BDI-21 scores in the Parc2011Yeo7 limbic system and ventral visual attention network in the right hemisphere during both resting state and Go/NoGo task. During the Go/NoGo task alpha LRTCs correlated with BDI-21 scores also in the left frontoparietal and dorsal visual attention networks (Figure 5B).

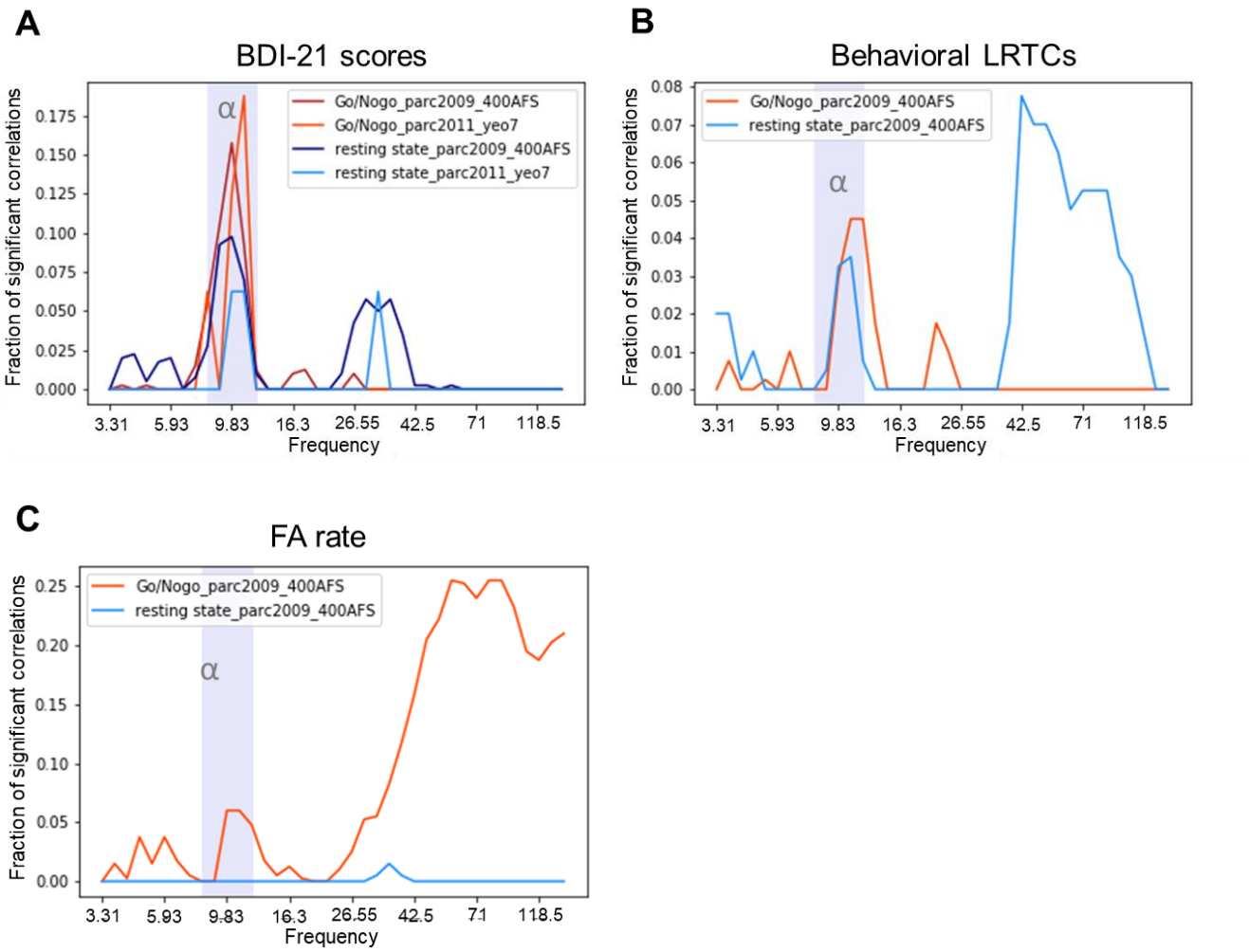

Figure 4. Fraction of significantly correlating parcels and networks in different frequencies in both conditions ($p<0.05$, FDR CORRECTED, one-tailed Spearman rank correlation). **A)** Fraction of significant correlations between source time series and BDI-21 scores. Significant correlations were found predominantly in the frequencies in the alpha range (8–12Hz). **B)** Fraction of significant correlations between source time series and Go/NoGo reaction time time series. Significant correlations were found in the frequencies in the alpha range (8–12Hz) in the parc2009 400AFS parcels in both conditions, but not in Yeo7 functional networks. Also, gamma band frequencies had a high fraction of significantly correlating parcels. **C)** Fraction of significant correlations between source time series and false alarm rate in the parc2009 400AFS parcels. The highest fraction was observed in the low and high gamma bands, but significant correlations were found also in the alpha band in the Go/NoGo task. No significant correlations were found in the Yeo7 networks.

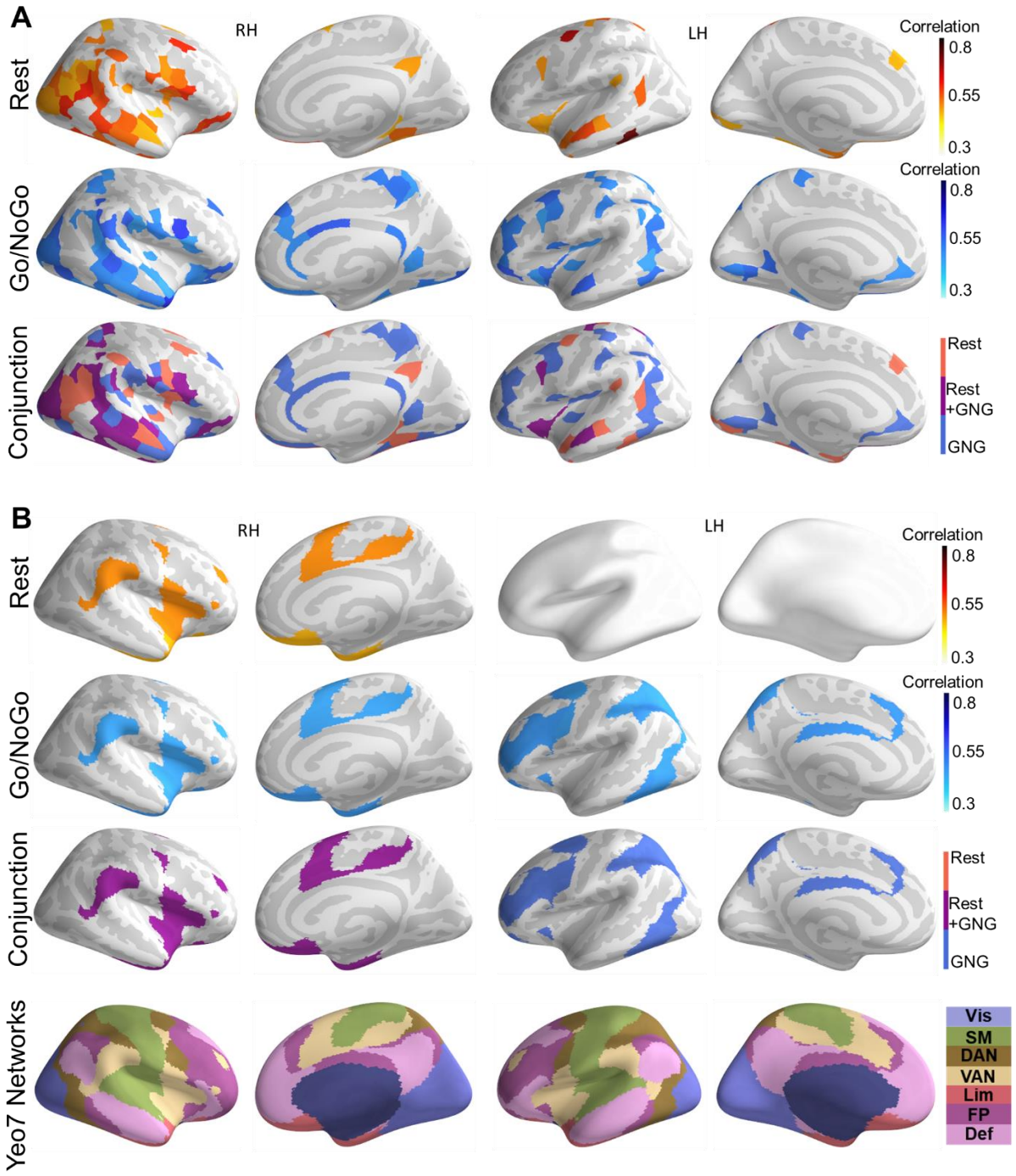

Figure 5. Average of the significant correlations between alpha band LRTCs and depression severity ($p<0.05$, FDR corrected, one-tailed Spearman rank correlation) during resting state and Go/NoGo task. Conjunction indicates the areas that reached significance in both conditions. **A)** Significant correlations in Parc2009 400AFS parcels in different conditions. Correlations were observed predominantly in occipital, temporal, parietal and orbital areas, and parts of the insula in both conditions. **B)** Significant correlations in Parc2011 Yeo7 functional networks in different conditions. Highest correlations were

observed in both conditions in the limbic system and ventral visual attention network in the right hemisphere. Prefrontal and dorsal attention networks in the left hemisphere correlated with BDI-21 in the Go/NoGo inhibition task but did not reach significance in resting state.

3.3. Alpha band LRTCs correlate with reaction time LRTCs in superior temporal area, circular insula, and right sub-central area

LRTCs in both conditions correlated also with the behavioral reaction time LRTCs in alpha band in the parc2009 400AFS parcels. No correlations were found in the Yeo7 functional networks. In the resting state the highest fraction of significant correlations was observed in the low-gamma band, but the analysis was restricted to alpha band frequencies based on the other comparisons where alpha band reached the highest fraction.

The highest fraction of significant correlations in alpha band was 0.035 (freq=10.92) (Figure 4B). The alpha band correlations in resting state were dominantly in the right hemisphere temporal and insular areas (Figure 6). In the Go/NoGo task, alpha band had the highest fraction of significant correlations, the highest being 0.045 (freq= 10.92 and 11.89 Hz) (Figure 5). In the inhibition task correlations were observed more in the left-hemisphere, concentrating on the temporal, orbital, parietal, occipital lobe and insular areas (Figure 6). Only 26% of the significant parcels in the resting state were also significant in the Go/NoGo task. These parcels were located on both hemispheres in the superior temporal area and circular insula, and in the right sub-central area (Figure 6).

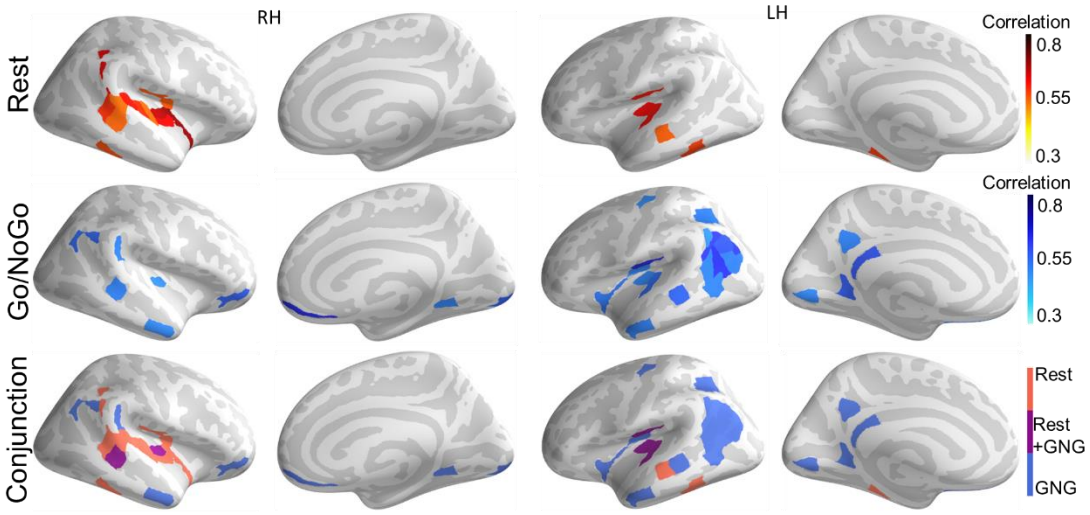

Figure 6. Average of the significant correlations between alpha band LRTCs and reaction time LRTCs ($p<0.05$, FDR corrected, one-tailed Spearman rank correlation,) during resting state and Go/NoGo task in the Parc2009 400AFS parcels. Conjunction reflects the areas that reached significance in both conditions. In the resting state correlations were mostly observed in the right hemisphere whereas in the inhibition task they were located more in the left hemisphere. Parcels in the superior temporal area and circular insula, and in the right sub-central area had significant correlations in both conditions.

3.4 Alpha LRTCs had a negative correlation with FA rates in the precuneus, cuneus, and parietal and occipital regions in Go/NoGo task.

Resting state LRTCs correlated with FA only in the beta/low-gamma band, the highest fraction of significant correlations being 0.015 (freq=31.5 Hz). In the Go/NoGo task, the highest fraction of significant correlations, 0.255, was also seen in the higher frequencies (freq=59.3, 78, 85.92 Hz), and in the alpha range the maximum fraction was 0.06 (freq=9.83 and 10.92 Hz) (Figure 4C). The parcels that correlated with alpha band frequencies were located in the precuneus, cuneus, and parietal and occipital regions.

No significant correlations with resting state LRTCs were found in Yeo7 functional networks in either of the conditions.

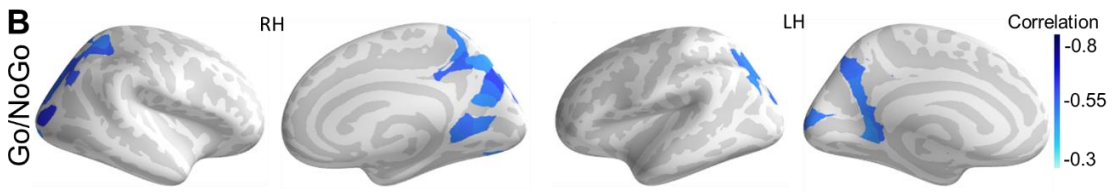

Figure 7. Average of the significant correlations between alpha band LRTCs and FA rates ($p<0.05$, FDR corrected, one-tailed Spearman rank correlation) Go/NoGo task in the Parc2009 400AFS parcels. Significant correlations were found in precuneus, cuneus, and parietal and occipital regions. No correlations in resting state alpha LRTCs and FA rates were found.

3.5 Alpha band LRTCs correlate with both depression severity and behavioral fluctuations in the insular, orbital, and temporal regions

There was overlap between the areas where alpha band LRTCs showed significant correlations with depression scores and RT LRTCs. In resting state, in 32% of the parcels where alpha LRTCs correlated with RT LRTCs, correlations with BDI-21 scores were also found. These parcels were predominantly located in the temporal areas.
In Go/NoGo, in 55% of the parcels where alpha band LRTCs correlated with RT LRTCs correlations with BDI-21 scores were also observed. These parcels were predominantly located in the orbital, insular and temporal regions.

Resting state alpha frequencies did not correlate with FA rates, but 28% of the parcels where alpha LRTCs correlated with FA rate in Go/NoGo task had correlations with BDI-21 scores. These parcels included parietal and occipital regions and parts of precuneus.

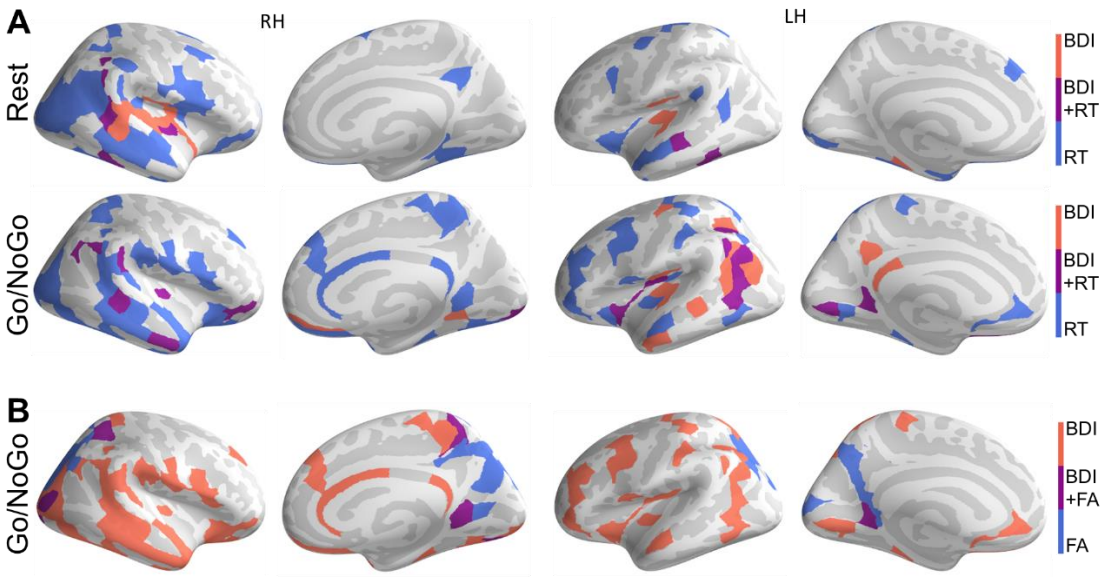

Figure 8. Parcels where alpha band LRTCs had significant correlations with depression severity and behavioral performance. Shared parcels are marked as purple. **A)** Parcels where alpha LRTCs correlated with BDI-21 and RT LRTCs. Shared parcels were found predominantly in the temporal regions in resting state and orbital, insular and temporal regions in Go/NoGo. **B)** Parcels where alpha LRTCs correlated with BDI-21 and FA rates in Go/NoGo task. Shared parcels were located in parietal and occipital regions and parts of precuneus.

4. Discussion

4.1 Increase in alpha band LRTCs in the limbic system is related to depression severity

We measured MEG resting state and Go/NoGo task activity from 19 depressed subjects and analyzed the correlations between depression severity (measured with BDI-21 questionnaire) and neural LRTCs on the source level in parc2009 400AFS parcels and Yeo7 functional networks. The correlations between LRTCs and depression were investigated in all frequencies and highest fraction of significant correlations after correction for multiple testing with FDR was observed in the alpha band (8–12Hz).

We found an increase in the alpha band LRTCs to be linked to depression severity in the limbic system that underlies emotional control. This could indicate that the limbic system

might be hyper-activated in depression, which could explain the negative bias characteristic to depression. The participants reported negative feelings especially during the Go/NoGo task, such as frustration towards the task and themselves, which could be reflected by the strong LRTCs in the limbic system even in the absence of emotional stimuli.

The Yeo7 limbic system includes orbitofrontal cortex and temporal pole, in which correlations between depression severity and alpha band LRTCs were also found on the analysis done on parcel level. In addition, alterations in the occipital, parietal and insular areas were associated with depression severity both during resting state and response inhibition. Depression has been previously shown to be linked to decreased gray matter volume in the orbitofrontal cortex, insula and temporal regions (Harada et al., 2016). Insula metabolism has been shown to be linked to responsiveness to selective serotonin reuptake inhibitor and cognitive behavior therapy (McGrath et al., 2013), and reduction in orbitofrontal activity and increased connectivity between OFC and posterior insula during loss has previously been linked to higher depression symptoms (Jin et al., 2017). The role of temporal pole dysfunction in depression is supported by observations of altered functional connectivity of temporal pole in medication-free MDD subjects (Zhang, Wu, Xu, & Shang, 2018) and by the effect of short mindfulness intervention which attenuated depression symptoms and decreased theta band LRTCs in the temporal region (Gärtner et al., 2017).

Our observations of the alterations in alpha band LRTCs in the limbic system, and in parcels located in the temporal pole, OFC, and insula, are in line with the previous findings about the depression-related functional and anatomical alterations in these regions that take part in the regulation of emotions.

4.2 Alterations also in the attentional and frontoparietal networks

In our study, positive correlations were also found in the frontoparietal network and ventral and dorsal attention networks that support cognitive control. Functional connectivity in frontoparietal network has previously been shown to be altered in MDD especially in non-

medicated depression, and medication was shown to return the connectivity to control levels (He, Y. et al., 2017). Frontoparietal network subsystems have been shown to control the default mode network and attention networks (Dixon et al., 2018), and the alterations in functional connectivity and our observation in the increased alpha band LRTCs indicate that alterations in top-down control of attention and emotion might be a key component in MDD.

Functional connectivity within ventral attentional networks has also been shown to be increased in adolescent depression, possibly explaining the attentional bias towards negative things in MDD (Liu et al., 2019). Neither of our conditions involved negative stimulus, but it can be hypothesized that the LRTCs might not always reflect the activity of the network in response to specific events, such as negative stimuli, but they might be more of a sign of the general deficits in these networks, such as the proposed deficits in E/I balance. Hence these alterations can also be seen in the absence of the stimuli that would normally activate for example ventral attentional network.

4.3 Alpha band LRTCs correlate with behavioral LRTCs but are more related to depression than increase in task performance

We also found correlations between alpha band LRTCs and reaction time LRTCs. It should be considered that the relationship between higher alpha LRTCs and depression severity could be explained by having cognitively well-performing severely depressed individuals in the cohort, as behavioral performance correlated with depression severity in our study and increase in behavioral LRTCs has previously been shown to have a positive correlation with behavioral performance in the Go/NoGo task (Simola et al., 2017). However, no correlation between reaction time LRTCs and FA rate was found in our study, indicating that the increase in alpha LRTCs is more linked to depression than increase in task performance.

High behavioral LRTCs in depression could possibly be explained by traits such as perfectionism or over-achieving that could lead to increased concentration in the more severe depression. However, the correlations between RT LRTCs and alpha LRTCs were also observed in the resting state, indicating that the variability in behavioral LRTCs stems

from the power-law guided brain dynamics as has been suggested by Palva et al. (2013), and the increase in RT LRTCs is probably not explained by increase in concentration but explained by the intrinsic brain dynamics.

4.4 Stronger link between alpha band LRTCs and depression severity during the Go/NoGo task than during resting state especially on the left hemisphere

Interestingly there were more significant correlations on left hemisphere in the Go/NoGo condition than in the rest condition in all comparisons. It has previously been shown that Go/NoGo task activates the brain bilaterally, but more in the left hemisphere frontal and parietal networks (Rubia et al., 2001). However, others have argued that the activation is more prominent in the right hemisphere, localizing to frontal areas, anterior insula, and parietal lobe (Garavan, Ross, & Stein, 1999) and prefrontal area (Konishi et al., 1999). In addition, orbitofrontal activation has been linked to behavioral and emotional inhibition in lesion studies in humans (D.T. Stuss & D-F. Benson, 1986; J.M. Fuster, 1989; Malloy, Bihrle, Duffy, & Cimino, 1993; Rolls, Hornak, Wade, & McGrath, 1994). We observed differences between resting state and Go/NoGo task LRTCs correlations with RT LRTCs in the left hemisphere temporal, orbital, parietal and insular areas, and differences in correlations with depression severity were found in the left hemisphere frontal areas. The role of these areas in the inhibition of movement might partly explain why there were more correlations in these areas in the Go/NoGo conditions in comparison to the rest condition.

In general, the fraction of significant correlations was higher in the Go/NoGo task than in the resting state in all comparisons, and it is logical that there are more correlations in the Go/NoGo task alpha LRTCs with the measurements that are related to the task, such as the reaction time LRTCs and FA rate. It is interesting however, why a larger fraction of significant correlations of alpha LRTCs with depression severity was found in the Go/NoGo task in comparison to the resting state. It can be argued that maybe it is due to the relationship between depression severity and behavioral LRTCs, that in turn are related to brain LRTCs, and more so during the Go/NoGo task. However, participants reported negative feelings, such as frustration, only during the task condition, and hence it is also possible that the task condition activated networks that are related to difficulties in

emotional and cognitive processing in MDD, and more so especially in the participants with severe depression.

Alpha LRTCs in the Go/NoGo task had a negative correlation with FA rate, but not in the resting state. Correlations were found in the precuneus, cuneus, and parietal and occipital regions. Increased grey matter volume in cuneus and parietal lobule has been shown to correlate with better inhibitory control in Bipolar Disorder, type I (BDI) patients(Haldane, Cunningham, Androutsos, & Frangou, 2008). The authors speculate that the increase in grey matter in these areas might be a compensatory method to overcome the deficits in other networks in BDI, and the same might apply for our depression cohort.

Even though the alpha LRTCs correlated with the behavioral LRTCs and FA rate, it should be noted that the brain LRTCs had more significant correlations with BDI-21 score than with the behavioral measurements. This could indicate that depression is more of a network level disease, whereas the movement inhibition activity is more localized to certain areas, or that the task related activity is more affected in other frequency bands that were limited outside this study. Based on these results it can be argued that altered LRTCs in the alpha band are a good indication of depression severity. Alterations in LRTCs have been linked to imbalance between excitation and inhibition, connectivity and neuromodulation, and based on our results we can speculate that these mechanisms are altered especially in the limbic system, frontoparietal network and attentional networks, possibly also explaining the alterations in emotional regulation and cognitive control in MDD.

4.5 Comparison to other studies

Our data indicated that the highest fraction of significant correlations between neural LRTCs and depression severity was in the alpha frequency band and that the correlation was positive. Previous studies have found both increased and decreased LRTCs in MDD, and within varying frequency bands. Linkenkaer-Hansen et al. (2005) observed a slight positive correlation between alpha band LRTCs and depression severity in a cohort of 12 MDD subjects, and Bornas et al. (2014) found a negative correlation with depression

scores in a group of 28 sub-clinically depressed undergraduates. Our results support the findings of Linkenkaer-Hansen et al. (2015), and the conflicting result in the sub-clinical group might be explained by the differing brain dynamics in sub-clinical depression in comparison to MDD. In addition, the use of short window lengths in DFA analysis (0.1 – 6.0 seconds) might bias the scaling exponents (Hu et al., 2001; Kantelhardt et al., 2001) and this might explain the absence and conflicting direction of the significant alterations in the alpha band LRTCs in some of the previously done studies. Longer time windows (1 – 225 seconds) were used in our study in order to obtain more accurate estimates for the LRTCs. We also observed a higher number of significant correlations in the Go/NoGo task in comparison to the resting state. This might be one explanation why observations of altered alpha band LRTCs have been sparse in other studies, as others have only measured resting state activity.

Alterations have been previously shown to exist in the theta band and broad band (Bornas et al., 2015; Gärtner et al., 2017; Lee et al., 2007; Linkenkaer-Hansen et al., 2005), and our data also indicates that theta band LRTCs correlated with depression severity, but to a lesser extent than alpha. In addition to positive correlations, also a negative relationship has been observed in the theta and beta band (Linkenkaer-Hansen et al., 2005). However, it was later argued by the authors that the reduced LRTCs in MDD group could maybe be explained by the long duration of the eyes-closed state, as this might cause more alterations in the EEG because of increased sleepiness (Gärtner et al., 2017). Our data also indicated that there would be correlations between beta and low-gamma band LRTCs and depression severity, and these frequencies could be explored in the future.

The sources of the altered LRTCs have not been localized in the previous studies. The alterations have been observed in the sensors all over the cortex and the variation from study to study is vast. However, there were significant alterations in the temporal cortex in all of the studies where alterations were found, and temporal regions had significant correlations consistently also in our source-level analysis. This supports the role of the temporal cortex in MDD. In addition, we showed that on the level of functional networks the alterations are localized in the limbic system, attentional networks and frontoparietal network. We also showed that the increased LRTCs persist during task performance, and

that they can also be seen in the behavioral fluctuations, further supporting the link between increased LRTCs and MDD.

4.6 Study limitations

The sample size in this study was quite small (N=19) and the data contained noise that could not be explained or filtered. In addition, the HPI-signals were not filtered from the current data, and even if their signals are in very high frequencies, the effect of the signals to the alpha band cannot be excluded. In the current study, use of antidepressants or comorbidities such as anxiety and bipolar disorder were not used as exclusion criteria, and their effects on the results cannot be excluded. Antidepressant medication has previously been shown to not to affect LRTCs in MDD (Gärtner et al., 2017), but it should be noted that the effect might depend on the used antidepressants and the length of use. In addition, suicidal individuals were left out from the study, and hence the results do not reflect extreme stages of depression.

We are currently processing data from a bigger cohort with 28 new subjects and it will be interesting to see whether our results can be later verified. It has been estimated that a cohort of 400 depressed subjects would be required to reach 50% reproducible results in fMRI studies with heterogenic population (Xia et al., 2019) , and the same problem most likely also applies to MEG recordings. Collecting a cohort of 400 depressed subjects is hardly realistic with the current resources, so one possibility for restricting the variability would be to exclude all comorbidities and medication. However, this would make data collection extremely challenging.

This study was also limited by the variation in the timing of the questionnaires, because it was tied to the playing of a game that was tested as another part of the study. This problem has been corrected in the currently ongoing study. To verify the link between alterations in alpha band LRTCs and depression, differences between control group and depression cohort should be tested. However, people cannot be strictly grouped into depressed and healthy individuals, as the symptoms vary a lot from person to person and even “healthy” people experience depressive symptoms every now and then. Hence it can

be argued that it is also useful to test correlations between the altered dynamics and severity of the pathology.

Correlations with specific symptoms, such as anhedonia and rumination should be tested in the future, as MDD is a heterogenic pathology, and different symptoms are likely to have different neurobiological mechanisms. However, it can also be argued that the very basic mechanism that underlies the different symptoms is the same, but only manifests differently in different individuals based on intrinsic and timing dependent vulnerabilities, such as the stage of development during traumatic events, and experiences. Differences in the inhibition-excitation balance could be one of these mechanisms underlying the different symptoms, and as alterations in LRTCs have been suggested to be related to alterations in this balance, it can be argued that they are also good for studying a heterogenic cohort of depressed subjects.

5. Conclusions

These results indicate that depression is related to increased alpha band (8–12Hz) LRTCs and also increased behavioral LRTCs. However, interestingly depression severity also correlated with better performance in the Go/NoGo task in our cohort. It has been previously shown that increase in behavioral LRTCs in linked to better performance in Go/NoGo task (Simola et al., 2017), and we cannot say whether the increase in the alpha LRTCs is more related to depression severity or if more severely depressed individuals happened to have good cognitive capabilities in comparison to the moderately depressed subjects and hence also had higher LRTCs. However, there was more alpha range LRTCs correlations with BDI-21 score than with RT LRTCs, and no significant correlations were observed between RT LRTCs and FA rate. This indicates that the altered neural and behavioral LRTCs were more related to depression than to good performance.

Alpha band LRTCs were found to correlate with depression severity in the limbic system, frontoparietal network and ventral and dorsal attentional networks. This could be interpreted the way that moderate levels of alpha LRTCs would be more beneficial to the functioning of the networks, and that all alterations from the optimal level are bad for the

individual in general, leading to difficulties in regulating one's emotions because both emotional and top-down cognitive networks are altered. It could also be speculated that increased LRTCs are related to increased activity stemming from the imbalance between excitation and inhibition and that depressive symptoms, such as emotional reactivity to negative things, are related to the hyper-activity of the limbic system that regulates emotional control. Task performance correlated with depression severity in our cohort, so the increased LRTCs in the frontoparietal and attentional networks could also be an indication of better functionality of these cognitive networks in this specific cohort.

Altogether, depression seems to be linked to alterations in the alpha band LRTCs. Same mechanisms, such as imbalance between inhibition and excitation, changes in connectivity, and neuromodulation, have been suggested to underlie both MDD and alterations in brain LRTCs, and based on our results it can be argued that studying LRTCs can bring new insights into our understanding of the neurobiology of depression and hopefully new targets for intervention.

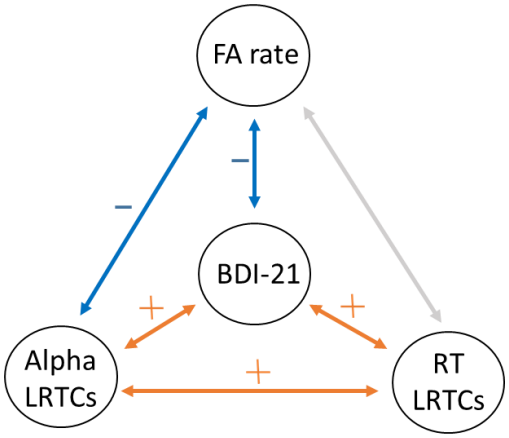

Figure 9. Summary of the correlations between depression severity, LRTCs in the brain dynamics and behavioral fluctuations, and behavioral performance. Depression severity had positive correlations with alpha band LRTCs and reaction time LRTCs, and negative correlations with FA rate, indicating that severe depression was related to better performance and higher LRTCs on both behavioral and brain activity level. Alpha LRTCs had negative correlations with FA rate and positive correlations with reaction time LRTCs. No significant correlations between RT LRTCs and FA rate were found, indicating that the

positive correlations between LRTCs and depression cannot be explained by good behavioral performance in the more severely depressed subjects.

References

Bak, P. (1996). *How nature works.* New York, NY: Copernicus.

Beck, A. T., Ward, C. H., Mendelson M., Mock J., & Erbaugh J. (1961). An Inventory for Measuring Depression. *Arch Gen Psychiatry, 4(6)* ,561–571. doi:10.1001/archpsyc.1961.01710120031004

Beggs, J. M., & Plenz, D. (2003). Neuronal avalanches in neocortical circuits. *The Journal of Neuroscience, 23*(35), 11167-11177. doi:10.1523/JNEUROSCI.23-35-11167.2003

Bell, A. J., & Sejnowski, T. J. (1995). An information-maximization approach to blind separation and blind deconvolution. *Neural Computation, 7*(6), 1129-1159. doi:10.1162/neco.1995.7.6.1129

Bhagwagar, Z., Wylezinska, M., Jezzard, P., Evans, J., Boorman, E., Matthews, P. M., et al. (2008). Low GABA concentrations in occipital cortex and anterior cingulate cortex in medication-free, recovered depressed patients. *International Journal of Neuropsychopharmacology, 11*(2), 255-260. doi:10.1017/S1461145707007924

Bornas, X., Fiol-Veny, A., Balle, M., Morillas-Romero, A., & Tortella-Feliu, M. (2015). Long range temporal correlations in EEG oscillations of subclinically depressed individuals: Their association with brooding and suppression. *Cognitive Neurodynamics, 9*(1), 53-62. doi:10.1007/s11571-014-9313-1

Bornas, X., Noguera, M., Balle, M., Morillas-Romero, A., Aguayo-Siquier, B., Tortella-Feliu, M., et al. (2013). Long-range temporal correlations in resting EEG. *Journal of Psychophysiology, 27*(2), 60-66. doi:10.1027/0269-8803/a000087

Bus, B. A., & Molendijk, M. L. (2016). The neurotrophic hypothesis of depression. [De neurotrofe hypothese van depressie] *Tijdschrift Voor Psychiatrie, 58*(3), 215-222. doi:TVPart_10797

Buzsáki, G. (2006). *Rhythms of the brain*. New York, NY, US: Oxford University Press. doi:http://dx.doi.org/10.1093/acprof:oso/9780195301069.001.0001

Caldji, C., Diorio, J., & Meaney, M. J. (2003). Variations in maternal care alter GABAA receptor subunit expression in brain regions associated with fear. *Neuropsychopharmacology, 28*, 1950. doi:https://doi.org/10.1038/sj.npp.1300237

Carceller, H., Perez-Rando, M., Castren, E., Nacher, J., & Guirado, R. (2018). Effects of the antidepressant fluoxetine on the somatostatin interneurons in the basolateral amygdala. *Neuroscience*, *386*, 205-213. doi: 10.1016/j.neuroscience.2018.06.041

Cavagna, A., Cimarelli, A., Giardina, I., Parisi, G., Santagati, R., Stefanini, F., et al. (2010). Scale-free correlations in starling flocks. *Proceedings of the National Academy of Sciences, 107*(26), 11865-11870. doi:10.1073/pnas.1005766107

Chialvo, D. R. (2010). Emergent complex neural dynamics. *Nature Physics, 6*, 744. doi:https://doi.org/10.1038/nphys1803

Dale, A. M., Liu, A. K., Fischl, B. R., Buckner, R. L., Belliveau, J. W., Lewine, J. D., et al. (2000). Dynamic statistical parametric mapping: Combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron, 26(1),* 55-67. doi://doi.org/10.1016/S0896-6273(00)81138-1

Dean, J., & Keshavan, M. (2017). The neurobiology of depression: An integrated view. *Asian Journal of Psychiatry, 27*, 101-111. doi:S1876-2018(16)30319-7

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage, 53(1),* 1-15. doi: 10.1016/j.neuroimage.2010.06.010

Dixon, M. L., De La Vega, A., Mills, C., Andrews-Hanna, J., Spreng, R. N., Cole, M. W., et al. (2018). Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. *Proceedings of the National Academy of Sciences, 115*(7), E1607. doi:10.1073/pnas.1715766115

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences of the United States of America, 96*(14), 8301-8306. doi:10.1073/pnas.96.14.8301

Gärtner, M., Irrmischer, M., Winnebeck, E., Fissler, M., Huntenburg, J. M., Schroeter, T. A., et al. (2017). Aberrant long-range temporal correlations in depression are attenuated after psychological treatment. *Frontiers in Human Neuroscience, 11*, 340. doi: https://doi.org/10.3389/fnhum.2017.00340

Gilden, D. L., Thornton, T., & Mallon, M. W. (1995). 1/f noise in human cognition. *Science, 267(5205),* 1837-1839. doi:10.1126/science.7892611

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., et al. (2014). MNE software for processing MEG and EEG data. *NeuroImage, 86*, 446-460. doi://doi.org/10.1016/j.neuroimage.2013.10.027

Gregoire, N., & Prigogine, I. (1977). *Self-organization in nonequilibrium systems: From dissipative structures to order through fluctuations*. Wiley.

Haldane, M., Cunningham, G., Androutsos, C., & Frangou, S. (2008). Structural brain correlates of response inhibition in bipolar disorder I. *Journal of Psychopharmacology, 22*(2), 138-143. doi:10.1177/0269881107082955

Hämäläinen, M. S., & Ilmoniemi, R. J. (1994). Interpreting magnetic fields of the brain: Minimum norm estimates. *Medical & Biological Engineering & Computing, 32*(1), 35-42. doi:10.1007/BF02512476

Harada, K., Matsuo, K., Nakashima, M., Hobara, T., Higuchi, N., Higuchi, F., et al. (2016). Disrupted orbitomedial prefrontal limbic network in individuals with later-life depression. *J Affect Disord., 204*, 112-119. doi://doi.org/10.1016/j.jad.2016.06.031

Hasler, G., van der Veen, Jan Willem, Tumonis, T., Meyers, N., Shen, J., & Drevets, W. C. (2007). Reduced prefrontal glutamate/glutamine and γ-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 64*(2), 193-200. doi:10.1001/archpsyc.64.2.193

He, B. J. (2011). Scale-free properties of the functional magnetic resonance imaging signal during rest and task. *The Journal of Neuroscience, 31*(39), 13786-13795. doi:10.1523/JNEUROSCI.2111-11.2011

He, Y., Lim, S., Fortunato, S., Sporns, O., Zhang, L., Qiu, J., et al. (2017). Reconfiguration of cortical networks in MDD uncovered by multiscale community detection with fMRI. *Cerebral Cortex, 28*(4), 1383-1395. doi:10.1093/cercor/bhx335

Herman, J. P., Renda, A., & Bodie, B. (2003). Norepinephrine–gamma-aminobutyric acid (GABA) interaction in limbic stress circuits: Effects of reboxetine on GABAergic neurons. *Biol Psychiatry, 53(2),* 166-74. doi://doi.org/10.1016/S0006-3223(02)01449-X

Hodkinson, D. J., Lee, D., Becerra, L., & Borsook, D. (2019). Scale-free amplitude modulation of low-frequency fluctuations in episodic migraine. *Pain,* doi:10.1097/j.pain.0000000000001619

Hosseinifard, B., Moradi, M. H., & Rostami, R. (2013). Classifying depression patients and normal subjects using machine learning techniques and nonlinear features from EEG signal. Comput *Methods Programs Biomed. 109(3),* 339-45. doi://doi.org/10.1016/j.cmpb.2012.10.008

Hu, K., Ivanov, P. C., Chen, Z., Carpena, P., & Stanley, H. E. (2001). Effect of trends on detrended fluctuation analysis. *Physical Review.E, Statistical, Nonlinear, and Soft Matter Physics, 64*(1), 011114. doi:10.1103/PhysRevE.64.011114

J.M. Fuster. (1989). *The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe*. New York, NY, US: Raven Press.

Jin, J., Narayanan, A., Perlman, G., Luking, K., DeLorenzo, C., Hajcak, G., et al. (2017). Orbitofrontal cortex activity and connectivity predict future depression symptoms in adolescence. *Biological Psychiatry.Cognitive Neuroscience and Neuroimaging, 2*(7), 610-618. doi:10.1016/j.bpsc.2017.02.002

Jovanovic, J. N., Thomas, P., Kittler, J. T., Smart, T. G., & Moss, S. J. (2004). Brain-derived neurotrophic factor modulates fast synaptic inhibition by regulating $GABA_A$ receptor phosphorylation, activity, and cell-surface stability. *The Journal of Neuroscience, 24*(2), 522-530. doi:10.1523/JNEUROSCI.3606-03.2004

Kantelhardt, J. W., Koscielny-Bunde, E., Rego, H. H. A., Havlin, S., & Bunde, A. (2001). Detecting long-range correlations with detrended fluctuation analysis. *Physica A: Statistical Mechanics and its Applications, 295*, 441-454. doi://doi.org/10.1016/S0378-4371(01)00144-3

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122*(5), 981-991. doi:10.1093/brain/122.5.981

Korhonen, O., Palva, S., & Palva, J. M. (2014). Sparse weightings for collapsing inverse solutions to cortical parcellations optimize M/EEG source reconstruction accuracy. *J Neurosci Methods, 226*, 147-160. doi:10.1016/j.jneumeth.2014.01.031

Lee, J. S., Yang, B. H., Lee, J. H., Choi, J. H., Choi, I. G., & Kim, S. B. (2007). Detrended fluctuation analysis of resting EEG in depressed outpatients and healthy controls. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 118*(11), 2489-2496. doi:S1388-2457(07)00405-1

Lin, F., Belliveau, J. W., Dale, A. M., & Hämäläinen, M. S. (2006). Distributed current estimates using cortical orientation constraints. *Human Brain Mapping, 27*(1), 1-13. doi:10.1002/hbm.20155

Linkenkaer-Hansen, K., Nikouline, V. V., Palva, J. M., & Ilmoniemi, R. J. (2001). Long-range temporal correlations and scaling behavior in human brain oscillations. *The Journal of Neuroscience, 21(4),* 1370-1377. doi:21/4/1370

Linkenkaer-Hansen, K., Monto, S., Rytsälä, H., Suominen, K., Isometsä, E., & Kähkönen, S. (2005). Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder. *The Journal of Neuroscience, 25*(44), 10131-10137. doi:10.1523/JNEUROSCI.3244-05.2005

Linkenkaer-Hansen, K., Smit, D. J. A., Barkil, A., van Beijsterveldt, Toos E. M., Brussaard, A. B., Boomsma, D. I., et al. (2007). Genetic contributions to long-range temporal correlations in ongoing oscillations. *The Journal of Neuroscience, 27*(50), 13882-13889. doi:10.1523/JNEUROSCI.3083-07.2007

Liu, J., Xu, P., Zhang, J., Jiang, N., Li, X., & Luo, Y. (2019). Ventral attention-network effective connectivity predicts individual differences in adolescent depression. *Journal of Affective Disorders, 252*, 55-59. doi:S0165-0327(18)31820-2

Luscher, B., Shen, Q., & Sahir, N. (2011). The GABAergic deficit hypothesis of major depressive disorder. *Molecular Psychiatry, 16*(4), 383-406. doi:10.1038/mp.2010.120

Malamud, B. D., Morein, G., & Turcotte, D. L. (1998). Forest fires: An example of self-organized critical behavior. *Science, 281*(5384), 1840. doi:10.1126/science.281.5384.1840

Malloy, P., Bihrle, A., Duffy, J., & Cimino, C. (1993). The orbitomedial frontal syndrome. *Arch Clin Neuropsychol., 8(3),* 185-201. doi://doi.org/10.1016/0887-6177(93)90035-Y

McGrath, C. L., Kelley, M. E., Holtzheimer, P. E.,III, Dunlop, B. W., Craighead, W. E., Franco, A. R., et al. (2013). Toward a neuroimaging treatment selection biomarker for major depressive Disorder. *JAMA Psychiatry, 70*(8), 821-829. doi:10.1001/jamapsychiatry.2013.143

Montez, T., Poil, S., Jones, B. F., Manshanden, I., Verbunt, J. P. A., van Dijk, B. W., et al. (2009). Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage alzheimer disease. *Proceedings of the National Academy of Sciences, 106*(5), 1614-1619. doi:10.1073/pnas.0811699106

Nikulin, V. V., & Brismar, T. (2004). Long-range temporal correlations in alpha and beta oscillations: Effect of arousal level and test–retest reliability. *Clin Neurophysiol., 115(8)*, 1896-908. doi://doi.org/10.1016/j.clinph.2004.03.019

Nikulin, V. V., Jönsson, E. G., & Brismar, T. (2012). Attenuation of long-range temporal correlations in the amplitude dynamics of alpha and beta neuronal oscillations in patients with schizophrenia. *NeuroImage, 61(1),* 162-169. doi://doi.org/10.1016/j.neuroimage.2012.03.008

Oostenveld, R., Fries, P., Maris, E., & Schoffelen J-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience, 2011*. doi:10.1155/2011/156869

Palva, J. M., Zhigalov, A., Hirvonen, J., Korhonen, O., Linkenkaer-Hansen, K., & Palva, S. (2013). Neuronal long-range temporal correlations and avalanche dynamics are correlated with behavioral scaling laws. *Proceedings of the National Academy of Sciences of the United States of America, 110*(9), 3585-3590. doi:10.1073/pnas.1216855110

Parish, L. M., Worrell, G. A., Cranstoun, S. D., Stead, S. M., Pennell, P., & Litt, B. (2004). Long-range temporal correlations in epileptogenic and non-epileptogenic human hippocampus. *Neuroscience, 125*(4), 1069-1076. doi:10.1016/j.neuroscience.2004.03.002

Peter Hansen, Morten Kringelbach, Riitta Salmelin. (2010). *MEG: An introduction to methods.* Oxford Scholarship Online.

Pfeffer, T., Avramiea, A., Nolte, G., Engel, A. K., Linkenkaer-Hansen, K., & Donner, T. H. (2018). Catecholamines alter the intrinsic variability of cortical population activity and perception. *PLoS Biology, 16*(2). doi:10.1371/journal.pbio.2003453

Poil, S., Hardstone, R., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2012). Critical-state dynamics of avalanches and oscillations jointly emerge from balanced excitation/inhibition in neuronal networks. *The Journal of Neuroscience, 32*(29), 9817-9823. doi:10.1523/JNEUROSCI.5990-11.2012

Rolls, E. T., Hornak, J., Wade, D., & McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery and Psychiatry, 57*(12), 1518-1524. doi:10.1136/jnnp.57.12.1518

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., et al. (2001). Mapping motor inhibition: Conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage, 13(2),* 250-61. doi://doi.org/10.1006/nimg.2000.0685

Sanacora, G., Gueorguieva, R., Epperson, C. N., Wu, Y., Appel, M., Rothman, D. L., et al. (2004). Subtype-specific alterations of γ-aminobutyric acid and glutamatein patients with major depression. *Archives of General Psychiatry, 61*(7), 705-713. doi:10.1001/archpsyc.61.7.705

Sanacora, G., Mason, G. F., Rothman, D. L., Behar, K. L., Hyder, F., Petroff, O. A. C., et al. (1999). Reduced cortical γ-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 56*(11), 1043-1047. doi:10.1001/archpsyc.56.11.1043

Shen, Q., Lal, R., Luellen, B. A., Earnheart, J. C., Andrews, A. M., & Luscher, B. (2010). γ-A.minobutyric acid-type A receptor deficits cause hypothalamic-pituitary-adrenal axis hyperactivity and antidepressant drug sensitivity reminiscent of melancholic forms of depression. *Biol Psychiatry, 68(6),* 512-20. doi://doi.org/10.1016/j.biopsych.2010.04.024

Shew, W. L., Yang, H., Yu, S., Roy, R., & Plenz, D. (2011). Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. *The Journal of Neuroscience, 31*(1), 55-63. doi:10.1523/JNEUROSCI.4637-10.2011

Simola, J., Zhigalov, A., Morales-Muñoz, I., Palva, J. M., & Palva, S. (2017). Critical dynamics of endogenous fluctuations predict cognitive flexibility in the go/NoGo task. *Scientific Reports, 7*(1), 2909. doi:10.1038/s41598-017-02750-9

Stuss D.T., & Benson D-F. (1986). *The frontal lobes*. New York, NY, US: Raven Press.

Taulu, S., & Simola, J. (2006). Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Physics in Medicine and Biology, 51*(7), 1759-1768. doi:S0031-9155(06)09790-9

Taulu, S., & Kajola, M. (2005). Presentation of electromagnetic multichannel data: The signal space separation method. *Journal of Applied Physics, 97*(12), 124905. doi:10.1063/1.1935742

Thomas Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology, 106*(3), 1125-1165. doi:10.1152/jn.00338.2011

Xia, M., Si, T., Sun, X., Ma, Q., Liu, B., Wang, L., et al. (2019). Reproducibility of functional brain alterations in major depressive disorder: Evidence from a multisite resting-state functional MRI study with 1,434 individuals. *Neuroimage, 189*, 700-714. doi://doi.org/10.1016/j.neuroimage.2019.01.074

Zhang, L., Wu, H., Xu, J., & Shang, J. (2018). Abnormal global functional connectivity patterns in medication-free major depressive disorder. *Frontiers in Neuroscience, 12*, 692. doi:https://doi.org/10.3389/fnins.2018.00692

Supplementary Materials

Table 1. Previous observations of statistically significant alterations in LRTCs in depression.

Study	Cohort	Females/ males	Mean age (sd)	Depression evaluation	medication	Comorbidities excluded	Method	Frequencies	DFA fitting range	Condition	Difference between MDD and controls	Relation to depression severity
Linkenkaer-Hansen et al. (2005)	12 MDD, 10 age-matched HC	5/7	44 (14)	HDRS-17 >= 18. DSM-IV.	Not in past 2 weeks	Yes	MEG, only gradiometers used (N=204). Analysis restricted to occipitoparietal and LH/RH temporocentral regions. Sensor space.	Theta (3-7), alpha (7-13), beta (15-29 Hz)	5-100s	16-min eyes-closed resting state	Attenuated LRTCs in theta and beta range in MDD. Differences in beta LRTCs were restricted to temporocentral regions.	Depression severity has negative correlation with theta LRTCs in the left termporocentral region, and slight positive correlation with alpha LRTCs in the occipitoparietal region. Theta LRTCs close to theoretical value of 0.50 for uncorrelated data in MDD group.
Lee et al. (2007)	11 MDD , 11 age-matched HC	9/2	44 (11)	BDI score ⩾10 and a HDRS score ⩾14 at intake. DSM-IV.	not in past 4 weeks (8 weeks for fluoxetine)	Yes	EEG, 8 channels. Sensor space.	Broad band (0.6-46 Hz)	0.1-0.6 s	5 min eyes-closed resting state	higher LRTCs in MDD in F3, C3, T3, T4 and O1 channels	Linear correlation between BDI score and scaling exponents over most of the cortex
Hosseinifard et al. (2013)	45 MDD, 45 HC	23/22	33.5 (10.7)	BDI >=10. DSM-IV.	No	No	EEG, 19 channels. Sensor space.	Delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz)	?	5 min eyes-closed resting state	No significant difference between MDD and HC DFA values.	-
Bornas et al. (2013)	56 ND	?	?	No screening for depression	?	?	EEG. Sensor space.	Broad band (1-40 Hz), theta (3-7 Hz), alpha (8-13 Hz)	0.1-0.6 s	resting state	-	Depression scores and negative emotion regulation strategies correlate with broad band LRTCs in central regions and theta LRTCs in parietal, occipital, and central regions.
Bornas et al. (2014)	28 subclinically depressed, 92 ND	22/6	26.39 (8.09)	PHQ9>4, BDI-II, ADIS-IV. Clinically depressed patients were excluded.	No	Yes	EEG, 10 channels. Sensor space.	Broad band (1-40 Hz), theta (3-7 Hz), alpha (8-13 Hz)	Broad band: 0.1-0.6 s. Narrow band: 1-6 s	8 min resting state consisting of 2 min intervals of eyes-open and -closed.	No difference between HC and SBD	Broad band LRTCs correlate with depression scores in central and parietal areas. Positive correlation between depression scores and theta LRTCs in parietal sites, and negative correlation with alpha LRTCs in frontal, central and occipital and temporal regions. Also brooding and thought suppression are related to broad band, theta, and alpha LRTCs in termporal, frontal, central, parietal and occipital areas.
Gärtner et al. (2017)	74 MDD (valid EEG data for N=71 pre-treatment, N=65 post-treatment, 25 HC	39/36	MDF: 41.6 (12.8) STR: 42.3 (11.8)	BDI II > 19. Lifetime history of MDD. DSM-IV.	Yes	Yes	EEG, 32 channels. Sensor space.	Theta (4–7 Hz), alpha (8–13 Hz), beta (15–25 Hz)	5-50 s	10 min eyes-closed resting state	Higher LRTCs in theta range in MDD in mid and left frontal as well as left temporal electrode sites	Attenuation of LRTCs after mindfulness training in central and temporal regions on LH. Reduction in BDI score correlated with reductions in theta LRTCs. Stress-reduction attenuatedd LRTCs in the fronto-parietal midline region, no correlation with symptom reduction.

Tests for depression: ADIS-IV = Anxiety Disorder Interview Schedule for DSM-IV (Lifetime version) (Di Nardo, Brown, & Barlow, 1994), BDI = Beck Depression Inventory (Beck & Beamesderfer, 1974), DSM-IV = Manual of Mental Disorders IV (APA, 2000), HDRS-17 = 17-item Hamilton Depression Rating Scale (Hamilton, 1960).
Participants: HC = Healthy control, MDD = Major Depression Disorder, SBD = Sub-clinically depressed
Treatments: MDF = Mindfulness meditation, SRT = Stress-reduction treatment